



## Original Research Article

## Impact of pre-operative vitamin D deficiency on post-operative outcomes in adult cardiac surgery

Rohit Malhotra<sup>1</sup>, Sambhunath Das<sup>1,\*</sup>, Minati Choudhury<sup>1</sup>, Neeti Makhija<sup>1</sup>, Sandeep Chauhan<sup>1</sup>, R Lakshmy<sup>2</sup><sup>1</sup>Dept. of Cardiac Anesthesia and Critical Care, All India Institute of Medical Sciences, New Delhi, India<sup>2</sup>Dept. of Cardiac Biochemistry, All India Institute of Medical Science, New Delhi, India

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## ABSTRACT

**Background:** Pleiotropic effects of Vitamin D (Vit D) on various cell types and causative association in the epidemiology of cardiovascular diseases is known for ages. Observational studies have successfully linked Vit D deficient states to critical illness and increased ICU morbidity and mortality. The role of preoperative Vit D deficiency on postoperative outcome in cardiac surgery patients is a new horizon for research.

**Methodology:** A prospective observational cohort study was planned to assess impact of pre-operative Vit D deficiency on post-operative cardiac outcomes in adult patients undergoing cardiac surgery, Vit D level was assessed in the preoperative period and divided into group I Vit D deficient (<20ng/ml) and group II Vit D sufficient (>20ng/ml). Primary outcome was to study the occurrence of myocardial infarction, arrhythmia, low cardiac output syndrome (LCOS) and inotropic requirement. Secondary outcomes were duration of mechanical ventilation, ICU length of stay, hospital stay and mortality.

**Result:** Vit D deficiency was associated with increased incidence of arrhythmia (p=0.019), LCOS (0.003) and high inotropic requirements (p=0.001) with no relation to occurrence of MI (p=0.422) and mechanical support (p= 0.114) as compared to the sufficient group. Vit D deficiency was also associated with increased duration of mechanical ventilation (p=0.008), ICU (p=0.001) and hospital stay (p=0.00) as compared to other group.

**Conclusions:** Vitamin D deficiency was associated with increased occurrence of arrhythmia, LCOS and high inotropic requirements. ICU morbidity in the form of increased duration of mechanical ventilation, ICU and hospital stay was increased in patients with Vit D deficiency.

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## 1. Introduction

Vitamin D has been known for ages as a key component for regulating calcium metabolism and bone structure in the human body. The pleiotropic effect of Vit D metabolites on various cell types like myocytes, fibroblast, osteoblasts, immune cells, neurons, vascular endothelial cells and cardiac myocytes is important for better functioning of human body.<sup>1,2</sup> Vit D undergoes hydroxylation inside

the human body to produce multiple metabolites and active form in the form of 1,25 dihydroxy Vitamin D [1,25(OH)<sub>2</sub>D]. Serum 25-hydroxy vitamin D [25(OH)D] levels act as perfect guide for Vit D status in the body.<sup>3</sup> The Institute of Medicine USA classified Vitamin D status on the basis 25(OH)D levels ranging from 50 nmol/L-125 nmol/L.<sup>4</sup> A level of Vit D <30nmol/L a re-emerging health hazard in the modern era that has led to rise in associated morbidity and mortality. Indian population is adversely affected by the epidemic of Vit D deficiency with levels varying from low serum concentration to undetectable in

\* Corresponding author.

E-mail address: [sambhunathds833@gmail.com](mailto:sambhunathds833@gmail.com) (S. Das).

blood.<sup>5</sup>

Role of Vitamin D in the epidemiology of cardiovascular diseases like hypertension, congestive heart failure, and sudden cardiac death has been an area of research in the recent times.<sup>6</sup> Various observational studies have successfully linked Vit D deficient states to increased incidence of cardiovascular diseases, critical illness and increased intensive care unit (ICU) morbidity and mortality.<sup>7–10</sup> Pre-operative Vit D status in patients undergoing cardiac surgery, a predictive marker for increased morbidity in the post-operative period is a broad horizon for research.

We conducted the study in patients undergoing cardiac surgery, to measure pre-op Vit D levels and compare the incidence of cardiac arrhythmias, myocardial infarction (MI), low cardiac output syndrome (LCOS), duration of mechanical ventilation, length of ICU stay, requirement for inotropic support and mechanical circulatory support in patients with abnormal Vit D levels.

## 2. Methodology

A Prospective observational cohort study was designed to study the impact of pre-operative Vitamin D deficiency on the post-operative cardiac outcomes in adult patients undergoing cardiac surgery. The primary objectives were to study the incidence of post-operative arrhythmia, MI, LCOS, requirement of high inotropic support and mechanical support. Secondary objectives were to study the duration of mechanical ventilation, ICU stay, hospital stay, in hospital death and any other adverse events during hospital stay.

All adult patients in the age group of 18-60yrs undergoing elective cardiac surgeries from January 2020 to June 2021 were included in the study group. Patients with age <18yrs and >60years; undergoing emergency surgery, Euro score II (>2), patients taking vitamin D or calcium supplements, patient undergoing aortic aneurysms and dissection surgery and refusal to be a part of the study were excluded.

Due to the ongoing COVID-19 Pandemic during study period a sample of cases were studied as per the availability of elective operative surgeries. After institutional ethical committee approval and after explaining the study protocol to the patient, a written and informed consent was taken. Vit D levels were measured preoperatively in all patients after admission to the hospital. Patients with vitamin D levels below 20ng/ml or 30nmol/L were labelled as vitamin D deficient (Group I) and any levels above these values as sufficient (Group II).

Intra and post-operative Period: Anaesthesia and surgery were standardized for all patients. In the perioperative period, patients were observed for occurrence of any new cardiac arrhythmias, use of high inotropic support (Vasoactive Inotropic Score [VIS] >10), use of mechanical

circulatory assist devices, occurrence of LCOS (Cardiac Index  $\leq 2.5$  L/min/m<sup>2</sup>), occurrence of MI (ST elevation >2mm), increased requirement for mechanical ventilation (>24 hrs), or increased length of stay in ICU (>48 hrs) and hospital (>7 days). Vasoactive inotropic score was calculated by adding the doses of inotropes received by the patient in the formula of; dopamine dose ( $\mu$ g/kg/min) + dobutamine dose ( $\mu$ g/kg/min) + 100  $\times$  epinephrine dose ( $\mu$ g/kg/min) + 10  $\times$  milrinone dose ( $\mu$ g/kg/min) + 10 000  $\times$  vasopressin dose (unit/kg/min) + 100  $\times$  norepinephrine dose ( $\mu$ g/kg/min). Incidences of these events were compared amongst patients with Vit D deficient and sufficient levels.

Inotropic requirement was estimated on the basis of VIS score and patients with score of more than 10 were labelled as high inotropic requirement. In Accordance with our institutional protocols most of the patients were extubated within 24hrs of surgery depending on the haemodynamic and general status. Any patient requiring mechanical ventilation more than 48 hrs was considered under prolonged ventilation. Patients were observed in the ICU post extubation for requirement of inotropes and rhythm abnormalities. Patients requiring ICU stay for more than 2 days were defined as prolonged ICU stay.

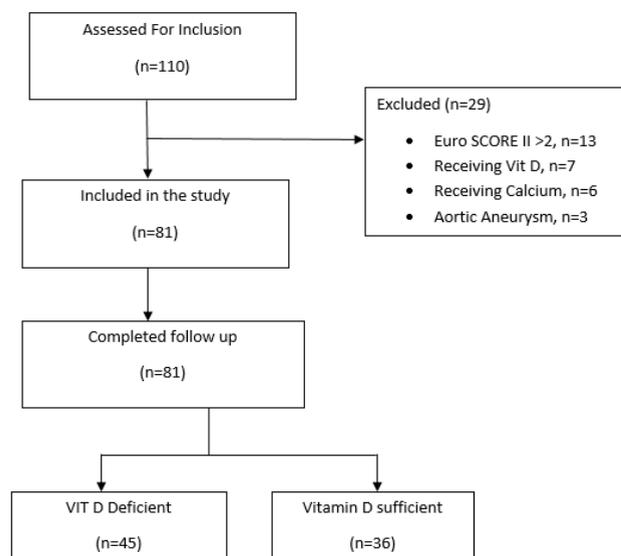
Transfer to step-down ward was done on decision of operating surgeon and ICU consultant in-charge. Discharge from the hospital was done after satisfactory recovery. Patients requiring hospital stay for more than 7 days had prolonged hospital stay. Any mortality post cardiac surgery among the study population during the hospital stay was considered under all-cause mortality.

Statistical analysis was done using STATA version 16. Mean and median were calculated for the given data set, significance level was adjunct with p value of <0.05. We checked for the normalcy of data. Continuous outcomes were analysed using student t test for parametric data. Mann Whitney/ Wilcoxin Rank sum test was used for analysing the non-parametric continuous outcomes. Categorical data was analysed using Chi square test.

## 3. Results

Out of total 110 patients only 81 patients were included in the study. Patients undergoing adult cardiac surgery were divided into two groups on the basis of preoperative Vit D Level as deficient (<20 ng/ml) and as sufficient Level (>20ng/ml). Out of the 81 patients studied 36 had sufficient serum levels compared to 45 deficient serum levels of vitamin D. (Figure 1) (Table 1)

Adult population included in the study had more males (n=47) compared to females (n=24), however vitamin D deficiency was not statistically different among the two. Study population had a mean age distribution of 40.17 yrs (SD  $\pm$ 13.87) among deficient group and 37.47 (SD $\pm$  13.97) yrs in the sufficient group. Mean weight was 56.15kg (SD $\pm$ 12.09) in the deficient group compared to 58.46kg (SD



**Fig. 1:** Study guideline

$\pm 13.34$ ) in the sufficient group. Mean height was 159.44cm and 162.25cm in the two groups respectively. Mean BMI was 22.12 kg/m<sup>2</sup> among the deficient group compared to 22.09 kg/m<sup>2</sup> in the sufficient group and with BSA of 1.56 and 1.61 in the two groups respectively. Study Population had a EuroScore II (Median IQR) of 0.94 in the deficient cases as compared to 0.67 in the sufficient group and this difference was statistically significant ( $p=0.017$ ). (Table 2)

Out of 81 patients only 50 underwent cardiac surgery on pump. Thirty patients in the Vit D deficient group required CPB during surgery with mean duration of 104.56 ( $\pm 39.55$ )min and clamp time of 71.63 ( $\pm 31.68$ )min. Twenty patients in sufficient group required CPB with mean duration of 102.85 ( $\pm 37.40$ )min and clamp time of 66.7 ( $\pm 28.16$ )min. Difference in CPB duration and Clamp time was not statistically different. (Table 3)

Vit D deficient cases postoperative MI ( $n=3$ ) was comparable to the sufficient group ( $n=1$ ), difference in outcome was also not statistically significant ( $p=0.422$ ). Post-operative arrhythmias were more common in patients with Vit D deficiency ( $n=9$ ) than patients with sufficient levels ( $n=1$ ). This difference among the two groups was statistically significant ( $p=0.019$ ). Occurrence of LCOS in patients with Vit D deficiency ( $n=10$ ) was significant between the two groups ( $p=0.003$ ). Three patients with Vit D deficiency required institution of intra aortic balloon pump (IABP) in the postoperative period.

Requirement for inotropes was decided on the basis of VIS. Patients with VIS > 10 were considered to have high requirements. Due to skewed distribution of the inotropic scores, non-parametric test of significance was applied. Mann-Whitney test was applied for analysis. Patients with Vit D Deficiency had more inotropic requirements as

compare to sufficient group,  $p=0.001$ .

Patients were shifted to the ICU post-surgery. Duration of mechanical ventilation and timing of extubation was variable on case basis and haemodynamic status post-surgery. Mean duration of mechanical ventilation was 15.21( $\pm 29.25$ )hrs for study population.

Patients with Vit D deficiency had increased duration of mechanical ventilation compared to sufficient group. Due to skewed distribution of the observation data, non-parametric test of significance was applied. Mann-Whitney test was applied for analysis where difference was statistically significant ( $p=0.00$ ). (Table 4)

Patients requiring mechanical ventilation for more than 24hrs were categorized under prolonged ventilation category. Eight patients in the Vit D deficient group required mechanical ventilation for >24hrs as compared to none in other group. The difference between the two groups was statistically significant.

Mean requirement for ICU stay was 4.84 $\pm$ 2.21 days in the Vit D deficient group compared to 3.02( $\pm 0.94$ ) days in the sufficient group. Forty-one patients in the deficient group required ICU stay for > 2 days as compared to 22 patients in the sufficient group. ICU requirement in the two groups was statistically significant ( $p=0.001$ ). Mean hospital stay in the deficient group was 11.17( $\pm 5.03$ ) days as compared to patients with sufficient Vit D levels 7.19( $\pm 2.08$ ) days. Difference between the two groups was statistically significant on t test analysis ( $t = -4.446$ ). Prolonged Hospital stay was defined for duration more than 7 days. Thirty-five patients in the deficient group and 11 patients in the sufficient group had prolonged hospital stay. Difference in stay was statistically significant. Three Patients in the Vit D deficient group died post-surgery, with no deaths recorded in the Vitamin D sufficient group. Difference was not statistically significant ( $p=0.114$ ).

**Table 1:** Basic characteristics

Variable	Vitamin D (<20 ng/ml) n=45	Vitamin D (>20 ng/ml) n=36
AGE (yrs)	40.17 ( $\pm 13.87$ )	37.47 ( $\pm 13.97$ )i
Weight (kg)	56.15 ( $\pm 12.09$ )	58.46 ( $\pm 13.34$ )
Height (cm)	159.44 ( $\pm 9.96$ )	162.25( $\pm 10.82$ )
BMI (kg/m <sup>2</sup> )	22.12 ( $\pm 4.84$ )	22.09 ( $\pm 3.92$ )
BSA	1.56 ( $\pm 0.19$ )	1.61 ( $\pm 0.22$ )

**Table 2:** Types of surgery

Type of Surgery	Vitamin D (<20ng/ml)	Vitamin D(>20ng/ml)	Total
Valve replacement	25	16	41
ASD and Primary Adult Congenital	7	12	19
CABG	12	7	19
Other	1	1	2

**Table 3:** Primary outcomes

Outcome	Vitamin D (<20ng/ml)		Vitamin D (>20ng/ml)		p Value
	Present	Absent	Present	Absent	
Arrhythmia	9	36	1	35	0.019
Myocardial Infarction	3	42	1	35	0.422
Low Cardiac Output	10	35	0	36	0.003
Mechanical Support	3	42	0	36	0.114
VIS (mean)	16.13±13.95		6.59±2.61		0.001
Total	25		2		

**Table 4:** Secondary outcomes [MEAN ± Standard Deviation]

Outcome (Days)	Vitamin D (<20ng/ml)	Vitamin D (>20ng/ml)	Statistical significance
Mechanical ventilation >24hrs	8	0	P=0.008
ICU Stay	4.84(±2.21)	3.02(±0.94)	-4.595
ICU Stay >2 Days	41	22	P=0.001
Hospital Stay	11.17(±5.03)	7.19(±2.08)	-4.446
Hospital Stay >7 Days	35	11	P=0.000

#### 4. Discussion

In the present study 55.6 percent of patients had Vit D deficiency. Deficient population presented more for valve surgeries followed by CABG. Preoperative Vit D deficiency was associated with adverse outcome in the form of postoperative arrhythmia, LCOS and high inotropic requirements. Prolonged hospital stay along with increased ICU morbidity was found more in patients with Vit D deficiency.

Vit D deficiency irrespective of age has been attributed to factors like ethnicity, socioeconomic status, sex, obesity, seasonal variation and environmental issues.<sup>4</sup> Mithal et al. reviewed global hypovitaminosis pertaining to different geographical regions and ethnicity.<sup>5</sup> They reported increased incidence of vitamin D deficiency in Indian population more common among younger age groups, females and population of urban areas. In contrast, in our study Vit D deficiency was equally distributed among both sexes and of equal age predisposition.

Euro score II is a logistic model to predict mortality post cardiac surgery in the preoperative period takes into consideration the patient characteristics like age, height, weight, BMI, sex; comorbidities like DM, hypertension, COPD; cardiac status characterized by ejection fraction, history of MI, pulmonary hypertension, peripheral vascular disease and type of cardiac surgery; along with renal function assessed by serum creatinine levels.<sup>11</sup> In our study Vit D deficiency was associated with a Euro score II of 0.94 in the study population that corresponded to increased morbidity and mortality in our observation. Zitterman et al also observed inverse association between Euro score and Vit D deficiency in their study on postoperative outcomes following cardiac surgery.<sup>10</sup>

Various observational studies have highlighted the significance of Vit D deficiency in pathogenesis of

cardiovascular diseases and risk association.<sup>12</sup> In our observational study more patients presented with valve disease in the Vit D deficient group as compared to patients with insufficient levels. Equal proportion of patients presented for bypass grafting and adult congenital heart defects in the deficient group. These results were similar to the study by Ney et al where patients with Vit D deficiency presented more for valve surgery as compared to isolated CABG.<sup>13</sup>

Vit D deficiency provides clinical evidence of increased plaque instability and incident myocardial infarctions.<sup>14</sup> In our study Vit D levels had no relation with occurrence of MI in the post-operative period, however these results were not consistent with the findings of Zitterman et al who observed increased incidence of adverse cardiovascular outcomes in the postoperative period.<sup>10</sup> Sriram et al also observed impaired cardiac function post cardiac surgery in Vitamin D deficient individuals post cardiac surgery.<sup>9</sup>

In the post cardiac surgery period arrhythmia are a common occurrence irrespective of the type of surgery and preoperative status. New onset atrial fibrillation (AF) are the most common arrhythmia following cardiac surgery having causative association with increased inflammation, renin angiotensin aldosterone system (RAAS) dysfunction and electrolyte imbalance.<sup>15</sup> Role of Vitamin D in regulating the immune function in the postoperative period along with inhibitory regulation of the RAAS axis leads the pathological basis of increased arrhythmia. Vit D deficient population in our study had increased occurrence of AF in the postoperative period. Metanalysis by Schneider et al emphasized the role of RAAS inhibition in incidence of AF.<sup>15</sup> Liu et al in a dose response analysis of 13 observational studies noted the association of Vit D deficiency with peri-operative AF.<sup>16</sup>

Low cardiac output syndrome and mechanical support: Impact of Vit D levels on the myocardial structure

and function has been attributed to the pleiotropic role. Decreased levels has been associated with increased myocardial hypertrophy, systolic and diastolic blood pressure alterations, and increased endothelial dysfunction.<sup>14</sup> Zeiterman et al in their observational analysis on incidence of major adverse cardiac and cerebral events (MACCE) reported increased incidence of LCOS in the postoperative period.<sup>8</sup> However, in their later analysis on hyper-vitaminosis of Vit D, they reported a U-shaped association with incidence of MACCE and Vit D levels.<sup>10</sup> In our study population with Vit D deficiency was associated with increased occurrence of LCOS in the postoperative as compared patients with sufficient levels. LCOS was defined by patient having cardiac output  $<2.5\text{L}/\text{min}/\text{m}^2$ , requiring inotropes to maintain BP  $>90\text{mmHg}$  and requiring IABP support to wean from CPB or postoperatively in ICU for hemodynamic stability. Contrary to our findings Sriram et al could not detect any correlation between Vit D deficiency and cardiac dysfunction.<sup>9</sup>

Down regulation of myocyte function along with cardiac instability and immunological impairment increases the inotropic requirement in the postoperative period to optimize organ perfusion and maintain stable hemodynamics. In our observation Vit D deficiency was associated with VIS of  $16.13\pm 13.95$  units suggestive of increased inotropic requirement post cardiac surgery. Javorski et al conducted a pilot study on 46 patients to assess the inotropic requirements, in post CPB period, for patients undergoing cardiac surgery. They reported increased vasopressor usage in patients with Vit D deficiency.<sup>17</sup> Ye X et al detected higher VIS of  $>15$  in children after cardiac surgery with preoperative Vit D deficiency.<sup>18</sup>

ICU morbidity: Co-morbid conditions and poor clinical status in the preoperative period are important determinants of outcomes in the post-surgery period. In our observation, patients with Vit D deficiency had prolonged requirement for mechanical ventilation and also increased duration of ICU stay. Role of Vit D in the maintaining good health of skeletal muscles enhancing their strength and tone is a key determinant for respiratory support in the critically ill.<sup>19</sup> Vit D deficiency has been associated with myopathy and neurological weakness along pathological basis of common respiratory ailments like asthma, COPD and lung fibrosis.<sup>20</sup>

Stimulation of inflammatory cascade and release of mediators are enhanced during cardiac surgery and post CPB exposure. Vit D receptors influence cascade through modulation of IL6 and IL8 function, along with maintaining a balance between pro-inflammatory and anti-inflammatory mediators.<sup>21</sup> Along with Impaired cardiac function, decreased Vit D levels are also responsible for susceptibility for critical ICU infections and organ dysfunctions.<sup>22</sup> Borgermann et al in their observational study on clinical outcomes post cardiac surgery in Vit D deficient people reported enhanced morbidity due to inflammatory processes and age associated issues.<sup>7</sup> In our

observation, Vit D deficient patients required mechanical ventilation for  $>24\text{hrs}$  and 41 patients stayed in ICU for  $>2$  days. Thirty-five patients with Vit D deficiency required hospital stay for  $>7$  days. Sriram et al observed significant association between preoperative Vit D levels with ICU and hospital stay post cardiac surgery.<sup>9</sup> Similar findings were reported by Zittermann et al in their analysis on clinical outcome post cardiac surgery where Vit D deficiency was associated with increased requirement for MV, prolonged ICU stay, hospital stay and increased morbidity.<sup>10</sup>

Vit D levels do influence the outcome of patients in the postoperative period mainly affecting the co-morbid disease status and response of the body to the surgical trauma.<sup>8,9</sup> In our observation three patients died in the Vit D deficient group however the cause of death was attributed to eventful operative period. To establish a causal relationship with mortality a larger population set is required.

The present study had few limitations. Firstly, due to the ongoing COVID-19 pandemic number of cases to validate the power of the study could not be recruited due to decreased number of elective cardiac surgeries. Secondly to estimate the incidence of cardiovascular events large numbers of cases need to be analysed. Third, association between Vit D deficiency and post-surgical outcomes could not be establish due to small sample size.

## 5. Conclusion

Vitamin D has a significant impact on the postoperative outcomes after cardiac surgery. In our study Vit D deficiency was associated with increased occurrence of arrhythmia, low cardiac output syndrome and high isotropic requirements. ICU morbidity was also increased in patients with Vitamin D deficiency in the form of increased duration of mechanical ventilation, ICU and hospital stay. Large cohort observational studies need to be planned to establish a causal association.

## 6. Source of Funding

None.

## 7. Conflict of Interest

The authors declare no conflict of interest.

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## Author biography

**Rohit Malhotra**, Senior Resident

**Sambhunath Das**, Professor  <https://orcid.org/0000-0001-5747-4811>

**Minati Choudhury**, Professor

**Neeti Makhija**, Professor

**Sandeep Chauhan**, Professor

**R Lakhsmy**, Professor

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